13 January 2003

201-14353B

ROBUST SUMMARY FOR SEC-BUTYL UREA

Summary

Sec-butyl urea is an odorless white crystalline solid with a sublimation point of 171°C, and an estimated boiling point of 224.95°C. Sec-butyl urea has a specific gravity of 0.25-0.28, estimated vapor pressure of 0.00294 mm Hg at 25ºC, and an estimated log Kow of 0.31. Sec-butyl urea has a water solubility value of 4 wt% at 20ºC.

Modeled data rank sec-butyl urea as being of low environmental concern for stewardship and regulatory action, which results from a low persistence score and a low score for bioaccumulation using the standard EPA emissions scenario of equal emissions to air, water, and soil. Predicted half-life in sediment, 140 days, indicates moderate persistence in this environmental compartment, but the estimated distribution based on Level III fugacity modeling predicts that sec-butyl urea will not partition into this compartment under tested release scenarios. Water and soil are predicted to be the major environmental compartments into which sec-butyl urea will partition. Estimated hydrolysis rates in water are slow. Estimated biodegradation rates indicate that this is a more important decay process in water. A worst-case scenario was also determined using EPIWIN v. 3.05. The 100% emission to soil scenario resulted in the longest half-life in soil (34 days). This half-life was also in the low persistence range (<2 months).

ECOSAR (Meylan and Howard, 1999) was used to estimate the missing aquatic toxicity data for sec-butyl urea to fish, *Daphnia* (planktonic freshwater crustaceans), and algae. Based on the fact that sec-butyl urea is produced at only one DuPont site in a closed system and ECOSAR predictions of an estimated 96-hour LC_{50} in fish of 1806 mg/L, an estimated 48-hour EC_{50} in *Daphnia* of 3184 mg/L, and an estimated 96-hour EC_{50} in green algae of 3339 mg/L, sec-butyl urea would be of low concern for toxicity to aquatic organisms. Substantiating these results are measured and ECOSAR results from an analogous compound, isobutylidene diurea. Measured aquatic toxicity data for this analog compound, as well as data estimated using ECOSAR, indicate that it is of low concern for toxicity to aquatic organisms.

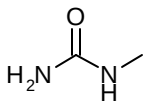
Compound	Algae, 96-hr EC_{50} (Estimated)	Daphnid, 48-hr EC_{50} (Estimated)	Fish, 96-hr LC_{50} (Estimated)
Sec-butyl urea	1806 mg/L[a]	3184 mg/L[a]	3339 mg/L[a]
Isobutylidene diurea	$1.56x10^5$ mg/L[b] >500 mg/L*	$3.09x10^5$ mg/L[b] >1000 mg/L*	$3.72x10^5$ mg/L[b] >1000 mg/L*

* Measured data.
[a] Log_{10} Kow of 0.31 used for modeling.
[b] Log_{10} Kow of –1.68 used for modeling.

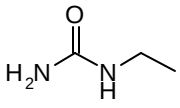
Sec-butyl urea has very low acute oral toxicity with an ALD of 7500 mg/kg in rats. Sec-butyl urea was a moderate eye irritant, producing temporary corneal injury, iritic congestion, and conjunctivitis when tested in rabbit eyes.

There is no developmental toxicity study available for SBU. Although the quantitative structure toxicity relationship (QSTR) model TOPKAT predicts that SBU would be a developmental toxin, literature on a closely related material suggests that SBU would not be a developmental toxin. When using such QSTR models, it is important to examine the training set of compounds from which the model is derived. The majority of the training set of structures the TOPKAT model is based upon thioureas that are known developmental toxins. One possible mechanism for the toxicity of thioureas is the formation of reactive sulfonyl metabolites during the oxidative desulfuration reaction. Under this mechanism, the corresponding ureas are not reactive, but are detoxification products of the thioureas. Therefore, using thioureas as the training set to build the QSTR model for the ureas is scientifically unsound and invalid.

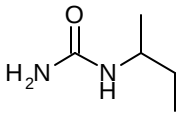
A study of the teratogenic effects of *N*-alkylureas (e.g., 1-methylurea, 1-ethylurea) found they are not teratogens, while their corresponding thioureas (1-methylthiourea and 1-ethylthiourea) are teratogenic (Teramoto et al., 1981). Using the closest neighbor analogy, we strongly believe that it is unlikely that SBU is a teratogen.



1-methylurea
(not a teratogen)



1 -ethylurea
(not a tetatogen)



sec-butylurea (SBU)

Based on the above scientific justification and using the scientific rationale consistent with the procedures described in the EPA Office of Pollution Prevention and Toxin technical document "The use of Structure-Activity Relationship (SAR) in the High Production Volume Chemical Challenge Program," no additional testing for developmental toxicity is necessary based on the following:

- **There is limited potential for exposure to SBU in quantities sufficient to produce effects**

SBU is a solid substance; the likelihood of exposure by the inhalation or dermal absorption route is negligible. It has very low toxicity by the oral route (rat oral ALD >7500 mg/kg). Information is presented that the potential for human contact in any substantial amount is quite low.

- **Alkyureas should not be grouped with alkylthioureas in the development of structure-toxicity activity relationship**

Teramoto et al., 1981 reported the relationship between the molecular structure of *N*-alkylureas and *N*-alkylthioureas and their teratogenic properties. Single maximum tolerated doses of 2000 mg/kg urea, methylurea, or ethylurea were given to pregnant rats on Day-12 of gestation. There were no significant differences from controls in mean number of implants, mean number

of live fetuses, percent fetal resorptions, mean fetal weight, or percent malformed fetuses. In contrast, a number of these parameters were affected by the corresponding thioureas.

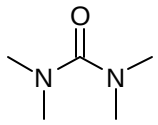
Two important observations were concluded:

1) The thiourea (C=S) moiety was essential for teratogenic potency.

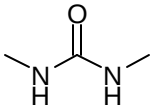
"There is one structural similarity between mono-alkylated thioureas and ETU which is essential for teratogenic potency. The C=S group is essential to mono-alklyated thioureas for manifesting teratogenic effects. Replacement of the C=S group with C=O (i.e., 1-methylurea or 1-ethylurea) resulted in the loss of teratogenicity."

2) The developmental toxicity of urea is related to the increasing number of methyl group attached.

Results from Teramoto's study are in agreement with the results reported by Von Kreybig et al., 1969, that "….teratogenic activity is enhanced by the increasing number of methyl group attached… 1,1,3,3-tetramethylurea , but not 1,3-dimethylurea, was teratogenic in rats…1,1,3,3-tetrametylurea is a strong teratogen toward the mouse fetus, where 1,3-dimethylurea was weak…."



1,1,3,3-tetramethylurea



1,3-dimethylurea

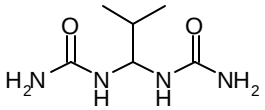
The teratogenic effects of the thioureas and methylated ureas are different. "…Thioureas affects CNS where as methylated urea malformations are detected in the palate, tail, and extremities…" Furthermore, the effect observed with the ureas decreases with the increasing alkyl moiety..."

These two research findings support the conclusion that *sec*-butylurea is unlikely to be a teratogen/development toxin, based on structural similarity to methylurea, ethylurea, and 1,3-dimethylurea. In view of the above observations, it is unlikely that SBU will exhibit the CNS or structural malformation effects exhibited by both the thioureas and methylated ureas.

- **Studies with structurally related alkyl ureas show no developmental toxicity**

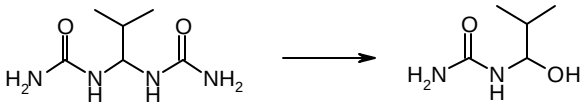
In addition to the study above in which rats were given large single doses during pregnancy, a traditional rat developmental study is available on isobutylidenediurea (IBDU, CAS #6104-30-9). The results of the developmental testing of IBDU are as follows. Wistar rats were given 0, 100, 400, or 1000 mg/kg IBDU in aqueous carboxymethyl cellulose suspension during days 6-15 of gestation (Hellwig, 1997; see also Section 6.3). There were no substance-related effects in dams (including body weight, body weight gain, food consumption,

clinical signs of toxicity, or reproductive data) at any dose level tested. There was no increased incidence of fetal malformations, variations, or retardations at any dose level tested. Therefore, the no effect level for the maternal and developing organism was 1000 mg/kg/day, the highest dose tested. IBDU was not a developmental toxin in rats.



N, N"-(Isobutylidene)bisurea
N, N" -(Isobutylidene)diurea
N,N"-(2-Methylpropylidene)bisurea
CAS# 6104-30-9

N,*N*-(isobutylidene)diurea (IBDU) is a diurea that would be metabolized *in vivo* via an *N*-dealkylation reaction to yield 1-hydroxy isobutylurea (IBU-OH), a close structural analog of SBU.



IBDU IBU-OH

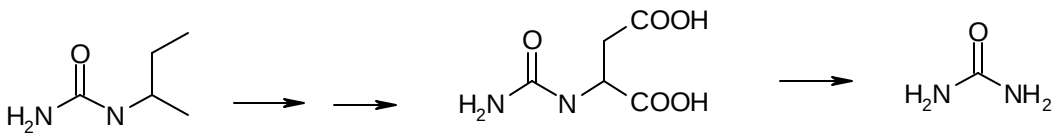
The close structural similarity between SBU and IBU also support the conclusion that SBU will be negative under same test condition as IBDU.

IBU SBU

IBDU/IBU can be considered as a suitable surrogate to testing SBU.

- **SBU could be expected to be metabolized to a naturally occurring substance, aspartic acid, in mammalian systems.**

C-Hydroxylation/oxidation of the methyl moieties are most likely biotransformations for SBU in mammalian systems to yield aspartic acid metabolites and eventually to yield urea (representative references, Quistad et al., 1988; 1982; Dua et al., 1996).



SBU L-aspartic acid metabolite

The catabolic transformation of SBU is therefore likely to produce metabolites that are that are natural components of biochemical pathways found in living organisms.

Therefore, DuPont proposes that no additional developmental toxicity testing is necessary for SBU based on available data for related materials. SBU is produced at only one DuPont site in a closed system. The physical nature of the material (solid and high water solubility) makes inhalation and dermal exposure unlikely. Since SBU is an industrial product not a consumer product, oral exposure is not expected.

Related alkyl ureas that have been evaluated are not developmental toxins. One of the alkyl ureas already evaluated, and found not to be developmentally toxic is IBDU. IBDU would be metabolized to IBU-OH, a close structural analog of SBU. Published information showed sec-butyl urea follows similar metabolic pathways with other structural similar compounds and no toxicity alert has been reported. SBU is expected to be metabolized to naturally occurring substances, aspartic acid and eventually urea.

Lastly, reliance on existing studies would prevent unnecessary wastage of animals. Therefore, it can be concluded, based on existing literature, that SBU is unlikely to be developmentally toxic.

No genetic toxicity information was found. Therefore, an *in vitro* bacterial reverse mutation assay and *in vitro* clastogenicity study in human peripheral blood lymphocytes following OECD Guidelines 471 and 473, respectively are proposed. As described below, the test material is a closed system intermediate; therefore, repeated dose and reproductive toxicity are not required.

Human Exposure

Sec-butyl urea (SBU) is manufactured at one DuPont facility (Belle Plant), and is shipped to only one customer. Sec-butyl urea, a white crystalline solid, is a raw material used in the production of a FIFRA registered herbicide. 100% of the sec-butyl urea is sold into this application. SBU is packed in bulk bags, placed on a cardboard sheet on pallets, and loaded in overseas shipping containers. There is no mixing of materials in the shipping containers--they only contain SBU. Manufacture of SBU is in a closed system, so that the only significant exposure risk is in loading and sealing the bulk bags and cleaning the dryer door. The loading operation is inside a building, and is essentially a closed operation, with a sock-type filter to remove powder from the exhaust air as the bag is filled. Since powder from the exhaust air is removed via filter, exposure to the test substance is not expected. Therefore, personal protective equipment (PPE) while filling bulk bags consists of dust resistant gloves. Cleaning the dryer door is performed approximately 5 times per shift, and 5 to 10 SBU bags are produced per shift. Any spills that result from bag loading are washed down to the on-site biological treatment plant. Process wastes from the manufacture of SBU are also treated at the on-site biological treatment plant.

Operators wear PPE as protection from leaks and spills when breaking lines or entering equipment for maintenance. This PPE consists of dust resistant gloves and goggles for breaking into lines. Equipment is normally wet-cleaned prior to entering equipment. However, if excessive dust is generated, a NIOSH approved air purifying respirator with particulate filters is worn.

The potential for exposure is the greatest during the loading and unloading of SBU, since closed processes are used at the sites. The sites can have from 2 to 5 personnel working (construction, contractor, and plant employees). The areas where the substance is manufactured will have from 1 to 2 operators during normal operations and 4 to 10 people during a shutdown. Equipment is wet cleaned so that dust generation is minimized. The site that produces SBU has effective safety, health and environmental practices and procedures in addition to engineering controls, environmental controls, and personal protective equipment to control exposure. Adequate safety equipment, such as safety showers, eyewash fountains, and washing facilities, are available in the event of an occupational exposure. Individuals handling SBU should avoid contact with eyes, skin, or clothing, should not breathe dust, and should wash thoroughly after handling.

The current customer for SBU, produced it from their own process for many years. DuPont conducted a contamination prevention audit at the customer's facility, and found that the customer's handling of the SBU included adequate controls.

Air monitoring has been conducted on SBU and results are shown in the table below. LOGAN (lognormal analysis) is a computerized statistical method for characterizing occupational exposures to chemicals, noise, and other environmental hazards. LOGAN uses sequential collection of data and makes decisions on the minimum amount of data. It helps make cost-effective, accurate decisions that ensure a healthy workplace. LOGAN uses inferential statistics to estimate the true workplace conditions, in the same way that public polling estimates opinions by sampling a representative percentage of the public. LOGAN is designed to limit the risk of employee occupational overexposure to less than 5%.

No specific exposure limits have been established for sec-butyl urea. The Workplace Environmental Exposure Level Guide (WEEL) for urea is 10mg/m^3, 8-hour TWA. None of the samples taken suggest the probability of exposure in excess of the WEEL for particulates.

EXPOSURE DATA

No. of Results	**Geometric mean (mg/m^3)**	**Min. of Results (mg/m^3)**	**Max of Results (mg/m^3)**
18[a]	0.143	<0.1	0.4
18[b]	0.133	<0.1	1.10

[a] Logan Analysis was performed on 4 of 18 sample. The conclusion of Logan analysis was "Acceptable."
[b] Logan Analysis was performed on 6 of 18 sample. The conclusion of Logan analysis was "Acceptable."

References for Summary:

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